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A NEW MODIFICATION OF BISCHLER-NAPIERALSKI REACTION FOR β-ARYLETHYLISOCYANATES AND β-ARYLETHYLURETHANS†

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Two-step treatment of β-arylethylisocyanates (1) and -urethans (2) with $POCl_3$ followed by $SnCl_4$ gave the corresponding dihydroisocarbostyrils (6) in satisfactory yields; the method was conveniently applicable to the hindered isocyanates and urethans with complex structure.

Bischler-Napieralski reaction is one of the most frequently employed method for synthesis of isoquinoline derivatives and a number of its modifications have been hitherto proposed.[2] None of them was, however, efficacious for cyclization of β-arylethylisocyanates (1) and β-arylethylurethans (2) to the corresponding 1-hydroxy-3,4-dihydroisoquinolines (dihydroisocarbostyrils), the yields of which were generally very poor except for few cases in

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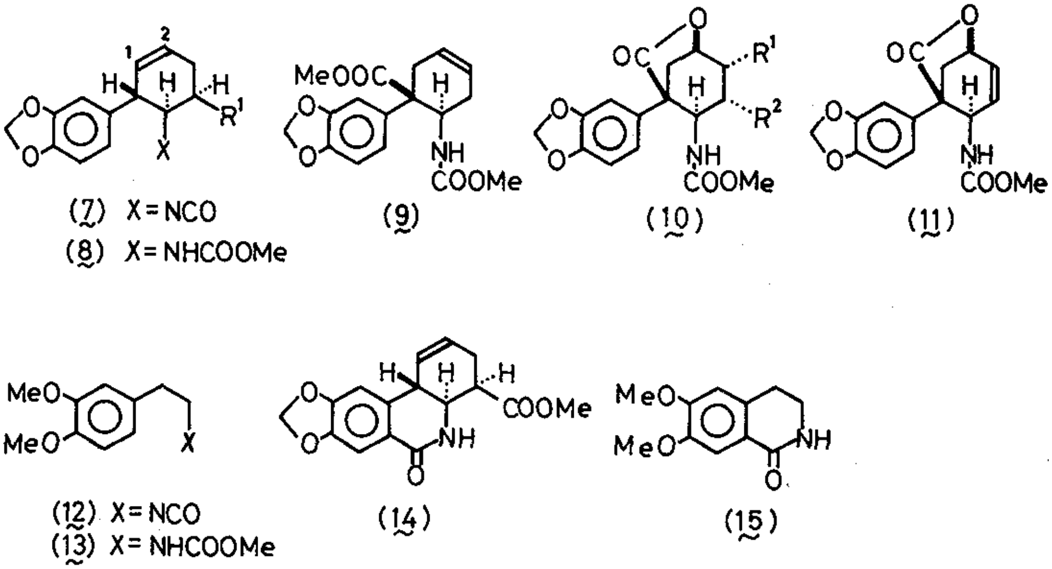
† Dedicated to Dr. Ken'ichi Takeda on the celebration of his seventieth birthday.

cyclization of β-arylethylisocyanates where PPA^3 or BF$_3$.Et$_2$O^4 was used as a condensing agent. We present here a new modification of Bischler-Napieralski reaction which permits cyclization not only of β-arylethylisocyanates but also of β-arylethylurethans generally in high yields. The cyclization of the latter is of great synthetic value since a carboalkoxy group is an excellent protecting group of amines.

During synthetic work^5 of the Amaryllidaceae alkaloid, lycorine, we found that the isocyanate (**7b**) smoothly cyclized to the dihydroisocarbostyril (**14**) in 70% yield by treatment with POCl$_3$ at 100°, and SnCl$_4$, whereas without pretreatment with POCl$_3$ the yield of **14** never exceeded 30% and heating with POCl$_3$ alone did not produce **14** to any noticeable extent.

The same two-step treatment for the urethan (**8c**) also produced the dihydroisocarbostyril (**14**) in 65% yield. Neither POCl$_3$ nor



(**7**) X=NCO
(**8**) X=NHCOOMe
(**9**)
(**10**)
(**11**)
(**12**) X=NCO
(**13**) X=NHCOOMe
(**14**)
(**15**)

Chart 1

$SnCl_4$ alone converted 8c to 14; the cyclization occurred on addition of $SnCl_4$ only after heating 8c with $POCl_3$.

We therefore applied this two-step procedure to several β-arylethylisocyanates and -urethans, all of which gave the corresponding dihydroisocarbostyrils (6) in satisfactory yields. - see Table 1.

Table 1. Modified Bischler-Napieralski cyclization of β-arylethylisocyanates and -urethans

Comp.	R^1	R^2	Pretreatment temp. with $POCl_3$	Dihydroisocarbostyrils yield(%)	m.p.
7a	H		100°	>90	280° (dec)
7b	-COOMe		100°	70	200-204°
8a	H		100°	47[a] (80)	280° (dec)
8b	H(1,2-dihydro)		100°	62	299-301°
8c	-COOMe		107°	65	200-204°
8d	$-CH_2COOMe$		107°	60	226-229°
9			150°	80[b]	292-295°
10a	Br	H	180°	44	>300°
10b	OAc	OAc	200°	60	>300°
11			180°	20	280-285° (dec)
12			107°	50 (83)[c]	178-181°
13			107°	60[d]	as above
13			150°	80[e]	as above

a) With recovery of 40% of starting material. Parenthesis indicates net yield.
b) Isolated via OMe-derivative, followed by hydrolysis with 50% AcOH.
c) Parenthesis indicates the yield when treated with $SnCl_4$ at room temperature.
d) After hydrolysis with 10% KOH.
e) Treatment with $POCl_3$ only, followed by hydrolysis with 10% KOH.

The reaction seems to proceed by initial activation of the urethan (2) to the phosphate (3) then to the isocyanate (1) and/or its activated species (4). The isocyanate (1) should also be reversibly activated to the same species (4) which cyclizes to the 1-hydroxy-3,4-dihydroisoquinoline derivative (5) on addition of $SnCl_4$; 5 will be easily hydrolysed to the corresponding dihydroisocarbostyril (6) during the isolation procedure. Intermediary formation of the isocyanate (7b) was indicated in the reaction of 8c by TLC and by the appearance of absorption at 2240 cm^{1} in the IR spectrum; quenching of the intermediate by MeOH regenerated the urethan (8c).

In some instances higher pretreatment temperatures were required for activation of urethans (e.g., 9, 10, 11). The urethan (11) yielded the expected dihydroisocarbostyril but in lower yield probably because of instability of an allyl-ester group.

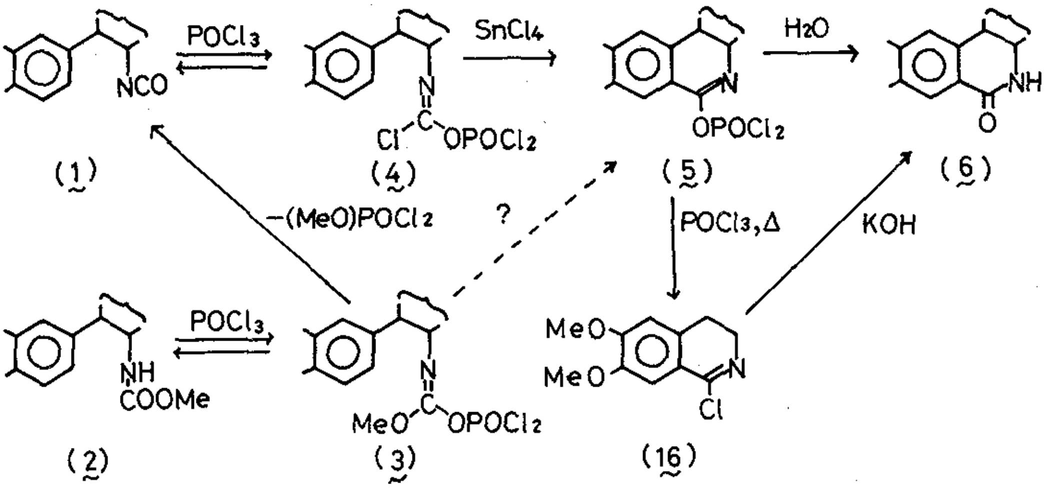
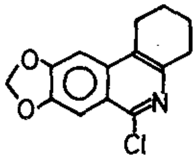


Chart 2

In cases of the simple unhindered β-arylethylisocyanate and -urethan, the results were somewhat different. The isocyanate (12) cyclized to the lactam (15) with $SnCl_4$ alone in 83% yield, pretreatment with

$POCl_3$ was unnecessary and did not improve the yield. For the urethan (13), treatment with $POCl_3$ alone at higher temperature was enough to effect cyclization even in the absence of $SnCl_4$. However, the product was accompanied with the compound supposed to be the 1-chloro derivative (16) and hydrolysis of the product with 10% KOH was necessary to obtain a satisfactory yield of the lactam (15). Thus heating of 13 with $POCl_3$ at 150° for 2 hr followed by extraction of the basified (NH_4OH) mixture with CH_2Cl_2 gave no lactam at all, but on hydrolysis of the product with 10% KOH for 3 hr afforded the desired lactam in 80% yield.

Elevation of the reaction temperature, however, sometimes produced undesirable side reactions. For example, heating of the urethan (8a) with $POCl_3$ at 150° afforded the aromatized compound (17), m.p. 203-204° in 46% yield. Therefore $SnCl_4$ is proved to be effective for carrying the reaction at moderate temperature.



(17)

The above results show that the method presented in this communication is more conveniently applicable to the hindered β-arylethylisocyanates and -urethans than to the unhindered compounds, thus being useful for syntheses of complex molecules such as natural products.

Details of the reaction mechanism will be discussed in a full publication.

REFERENCES and FOOTNOTES

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6. All compounds presented in this communication gave satisfactory elementary analyses and the spectral data supporting the expected structure.

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